Adjunctive therapies in the treatment of cancer

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Introduction

Although the title of this presentation would seem to imply that I am going to discuss multiple alternative therapies, I'm actually going to focus on the only alternative drug with which I have extensive experience, and that is the plant-derived immunostimulator, Helixor.

I think it would be useful to tell the story of how I was first introduced to this fascinating product. When I arrived back from my residency in the United States in late 1996 it became obvious that I needed to work hard in the field of cancer medicine. In Auckland and in fact the whole of New Zealand very little was being done in the way of chemotherapy compared to the USA. I also felt rather handicapped because tools such as radiation therapy and many of the investigational drugs that I was able to use in the USA were not available to me in New Zealand.

Dr Chris Piper, a veterinarian with an "alternative bent" had been importing the drug from Germany for several years and spoke to me about the product at some length. I must confess, as a conventionally trained internist I was somewhat dismissive of the drug. In the USA the internal medicine world at the time was very straight-laced and my training didn't really equip me to think laterally, at least not in the first instance.

Not long after Chris spoke to me I was presented with a very challenging case. It was an approximately eight year old male Weimaraner with a highly aggressive bilateral tonsillar squamous cell carcinoma (SCC). This had extended across the back of the oropharynx, had destroyed the tonsils and had left ugly bleeding holes in the soft palate. This tumour was biopsy-proven so there was no question about the diagnosis and even if we'd had every conventional medicine tool available under the sun I would have had to give the owners a very poor prognosis. The same would be true even today.

I thought, 'this is a perfect case for Helixor.' In the back of my mind I figured; 'well, the dog will go ahead and die and then I can write Helixor off as useless, which fits with my prejudices and I can get on with my conventional medicine career'.

Remarkably, over a period of 6-8 weeks the dog was completely cured. I couldn't believe what I was seeing and the owners kindly allowed me to re-biopsy the affected areas. The biopsies came back clean and although the soft palate still had a hole in it, it was pink and healthy with smooth edges. The tonsils had completely disappeared but the walls of the oropharynx were smooth and healthy-looking. This dog went on to live at least five more years and died of a combination of old age and heart disease, at which time he was still cancer free.

Now, a cynic would say that this dog is one of the rarely-recorded self-cures in a patient with malignant cancer. These are very uncommon, but they do occur in human and veterinary medicine. However, it just seemed too coincidental to me and given that Helixor is known in human medicine to be an immunostimulator, I was quite prepared to attribute the successful treatment to the drug.

I've since used Helixor in approximately 350 canine patients and probably about 20 feline patients, although I have not treated a cat with the drug for over 10 years. I'll explain why later. I can say without hesitation that the drug is a reliable stimulator of the immune system. What I cannot say for sure is; *which* dogs with *which* cancers are going to get benefits from the drug.

Assessing alternative products

Although I am probably one of the most open-minded of internists when it comes to alternative therapies, I do try to as much as possible be faithful to my training as a scientist, both during undergraduate studies at Massey University and as a resident doing formal research projects during my residency.

From an internal medicine perspective my impression is that very few people around the world who are promoting alternative therapies are prepared to do the research to produce incontrovertible proof that unconventional therapies from Helixor to homeopathy to naturopathy actually work.

The scientific method of a double-blind placebo-controlled trial is well established in human and veterinary literature and until someone comes along with a better way of assessing the efficacy of a therapeutic intervention, we should be considering these trial techniques for any therapy or procedure.

I freely admit that I've used Helixor in hundreds of dogs without proof that it actually works. It's important that those who read these notes or attend the presentation understand that I am telling a bunch of stories. I am not presenting robust clinical data. There is of course a place for anecdotes and the opinions of "experts", but these are regarded as low grade evidence. They should never replace the high grade evidence obtained from double-blind placebo controlled trials and the even more robust data obtained when the results of multiple trials are results assessed in a meta-analysis.

I remain puzzled and, in fact, mildly infuriated by the inability of alternative practitioners to see that they are never going to convince the majority of veterinarians or doctors if they refuse to subject their favoured treatments to scrupulous independent analysis. I have at times tried to formulate trials for Helixor but for reasons of logistics, economics, human resources and also mental health (☺) I have been unable to construct a satisfactory trial. Additionally, I've used the drug in over 30 different types of cancer so gaining the necessary 50-100 cases to achieve statistical significance in any one cancer would be difficult in the New Zealand environment.

I console myself that frusemide for the treatment of pulmonary oedema in dogs and cats has never been subjected to a modern clinical trial either, we just use it because we know it works. With regard to Helixor though, by all means be skeptical and be honest with your clients.

What is Helixor?

Helixor is a fluid that is prepared from the mistletoe plant (Viscum album). It is made by the Helixor company in Germany and has been used for around 40 years, however mistletoe extracts have been used against cancer since 1921 and the plant has been known to have medicinal properties for thousands of years. Remember Getafix the Druid in the Asterix comics harvesting mistletoe with his sickle?

In German-speaking countries it has been claimed that the product is the most commonly used alternative product in the treatment of cancer. In Germany they seem to have a more truly "holistic" approach to the treatment of cancer which means that a patient will have surgery, radiation, chemo, psychological support, diet and lifestyle advice as well as alternative therapies such as Helixor. The division between convention and unconventional medicine seems much more blurred there than it is here.

Helixor is not synthesized in a lab but is a filtered and modified extract of the plant. The properties of the plant vary from season to season so various harvests are made through the year and the material from each harvest is mixed to try to produce a consistent product. However there is still variation in the degree of immunogenic stimulus from batch to batch and as a clinician this takes some getting used to when compared to conventional medicines.

There are estimated to be several hundred molecules in the product, not all of which have been elucidated yet. The companies website states that it contains "first and foremost, certain mucilages (polysaccharides) and proteins (mistletoe lectins and viscotoxins), but also flavonoids (secondary plant compounds) and components of mistletoe paste (triterpenoids) are significant constituents of medicinal mistletoe extracts".

Extensive research has been done on the drug in human medicine, and a little in animal testing. The company makes the following claims about how the drug works.

Dose-dependent cytotoxicity in cell cultures by induction of apoptosis.

- Inhibition of tumour growth and metastases in animals.
- Immunomodulation: activation of macrophages, dendritic cells and natural killer cells, increase in phagocytosis and burst activity, increase in numbers of eosinophils, lymphocytes and T-helper cells.
- DNA stabilization in peripheral blood mononuclear cells resulting in a significant protection from immunosuppressive effects of chemotherapy.
- Inhibition of tumour angiogenesis.
- Release of ß-endorphins.

I have looked at quite a few abstracts from the human field and as far as I can tell these claims are in fact supported by the literature.

What is Helixor supposed to achieve for the patient?

In the human field there are two main areas of therapeutic claim for the drug. One is direct anticancer effect by a variety of mechanisms that lead to tumour regression, delayed tumour growth or stable disease.

The other claim is that when used alongside conventional therapies the drug reduces side effects of chemo and radiation, improves well-being, attitude and mobility in a variety of settings. For instance the drug has been proven in controlled trials to reduce the incidence of neutropenia in patients undergoing chemotherapy and this was statistically significant.

THE PLURAL OF ANECDOTE IS NOT DATA

What has been achieved in animals?

This is where I start talking about my own experience, which you must view as a sequence of anecdotes, not data. As the aphorism above so succinctly states it does not matter how many stories are told and no matter whom is telling the stories, they are still just stories unless they are tested in a double-blind placebo-controlled trial.

I am note sure how many patients Dr Chris Piper (now retired from clinical practice) has treated with Helixor but I am now at around the 350 patient level. As mentioned above I have been remiss in not keeping systematic records about these patients (as a cohort, they have the normal individual clinical record that any other patients will have) and so therefore my evidence is weak. It is possible that between Dr Piper and I have treated more animals than anyone else in the world.

I can say with 100% conviction that the drug is an immunostimulator. The clinical signs of immune system reaction are so reliable, so persistent in many cases and so repeatable from case-to-case that I have no doubt whatsoever that in the vast majority of dogs the drug will result in a reaction from the immune system.

What I cannot say is which dogs with which tumours will see anti-tumour benefit. We are providing a non-specific "wake-up call" to the patient's immune system and hoping that mixed in with the reaction to the many immunogenic molecules in the fluid there will be some anti-tumour activity.

This is different to specific immunotherapy for cancer such as the melanoma vaccine where we intend to provoke antibodies and cell-mediated immunity (CMI) against the melanoma cells but not against any other cells, normal or otherwise.

In my experience the "miracle cure" that I described in the introduction is by far the exception rather than the rule. I have had some other dogs with aggressive, unresectable metastatic tumours (anal sac adenocarcinoma, mast cell tumour, undifferentiated carcinoma, melanoma) go into complete remission but these would represent less than 10% of all the dogs that I have treated.

I think there must be a "God of Veterinary Medicine" who was looking down when I saw that first Weimaraner and thought "I'll teach this guy not to have such a closed mind!"

I estimate that 20-30% of dogs will show some measurable evidence of tumour regression. Evidence might be gained by palpation, ultrasonographic measurement of intra-abdominal lesions or radiographic assessment of pulmonary lesions. When Helixor is being used alongside conventional chemotherapy it is of course impossible to say which drug is doing the work but we see a number of cases where the results of combined therapy are much better than what we would expect from chemo alone. Also, because of the way Helixor produces reactions that can look like an episode of sepsis subsequent to neutropenia (fever, lethargy, anorexia – see later) I tend to use Helixor after chemo is finished or after the first few rounds have shown us what to expect. Usually by that time chemo has achieved most of what it is going to achieve and further gains could well be due to the Helixor.

30-40% of dogs show anti-tumour benefits that could best be described as delayed progression of the cancer of stable disease. In these dogs survival time is extended even though they still die of their cancer.

Some dogs show no benefit at all, especially when their cancer is very fast moving. The benefits or Helixor tend to take many weeks or even months to accrue so tumours such as hemangiosarcoma which typically kill within 60 days have not responded very well in my hands.

Non-specific benefits

I have lost count of the number of owners who report ancillary benefits of the drug. I don't tell owners to expect these, I am just intrigued as to how many will spontaneously volunteer the information. A repeatable phenomenon is that dogs with osteoarthritis will be more mobile, less stiff and less painful. Dogs that have not been able to jump in the car will jump freely and without pain. Other comments include more energy, playing games the pet has not for a year or more, shinier coat, brighter eyes, better appetite and just being mentally more alert. Frequently owners say that their dog seems younger than they have for ages.

These comments make me think that if I was in general practice I would really like to trial this drug in those geriatric dogs that have bad arthritis and seem to be becoming "senile" so that euthanasia for old age becomes the inevitable consequence.

I think these beneficial "side-effects" can be important in prolonging the lives of cancer patients. If a dog has a diagnosis of a fatal cancer and also is sore every morning, is starting to pee inside and is getting grumpy with the kids then euthanasia starts to look like the best option for many owners. If the cancer is stable, the dog's mobility improves and they seem happier all round then blue juice is not the inevitable consequence.

Which tumours have responded?

Mast cell tumour

In my hands the most reliable tumour response has been seen in mast cell tumour (MCT). I have had complete remissions that last years in dogs with metastatic unresectable Grade three MCT disease. In many cases dogs that have been showing repetitive growth of new and ever-more-aggressive MCTs show a dramatic reduction in the rate of developing new tumours, and fascinatingly the grade of tumour seems to reduce as well until the overall situation stabilizes.

I like to use Helixor alongside traditional therapies and also Palladia, the new drug for MCT. This is especially the case when the disease is very aggressive or advanced because of Helixor's slow onset of action. If the response is good and the dog is many months out with no evidence of active disease then I will reduce therapy to just the weekly maintenance Helixor.

I am very careful to assess in my own mind whether the drug is actually doing any good. MCT is a particularly tricky disease in this respect because sometimes incomplete resection of even quite aggressive lesions results in cure. This can occur despite a description from the pathologist that shows that tumour cells extend right to the edge of the resected lesion. This is a puzzling phenomenon and in dogs that receive no therapy other than surgery it probably represents an activation of the immune system leading to destruction of the remaining malignant mast cells without further intervention from the clinician. I am careful not to attribute benefit to Helixor in these situations, although I still recommend the drug.

I would use Helixor in any MCT patient that is growing repeated MCTs (of any grade), has an

incompletely resected mid- to high-grade MCT, has metastatic MCT or any visceral MCT lesion.

Nasal tumours

Nasal adenocarcinomas, chondrosarcomas, osteosarcomas etc are tumours which are very difficult to treat. Most owners are not willing to travel for radiation therapy (RT) and the chemo protocols we use, while they have improved in efficacy recently, still don't cure many dogs.

I have had some good successes in slowing down or stabilizing various nasal tumours, especially adenocarcinomas. I have had at least one dog with a nasal osteosarcoma (biopsy proven and confirmed by a second opinion) go into complete remission until the dog died years later of other causes.

Haemangiosarcoma (HSA)

As mentioned, this fast growing tumour is not ideally suited to treatment with Helixor due to the slow onset of action of the drug. However in a few cases we have been able to buy time with conventional chemo and then try Helixor. I had one Labrador with a massive abdominal wall HSA that was as big as a rugby ball and completely unresectable, (The owners were wealthy in this case but their vet made the classic mistake of saying "let's just wait and see if it grows"; over and over again!). I used an adriamycin/Helixor combo in this dog and we shrank the tumour by more than 60% (confirmed by ultrasound measurements) and the dog lived nine months until regrowth occurred. I cannot say for sure that the Helixor played a role here but the survival time was much better than anticipated with adria alone.

Anal sac and apocrine gland adenocarcinoma

I have had a number of dogs do well with this disease, including long lasting complete remission in a couple of dogs.

Lymphoma

I have seen one dog go into a seven-month remission from lymphoma with Helixor alone and then get a second remission of well over a year with chemo. Other dogs have show less dramatic benefits but have displayed a trend towards better chemo-tolerance.

Other cancers

I have treated many other cancers with the drug but not enough to make sweeping statements. I always offer conventional drugs with proven efficacy first and offer Helixor as either adjuvant treatment, or when the conventional drugs fail, or if conventional drugs are declined or if there is no possible conventional therapy. This means that Helixor comes up against the toughest tumours and yet we still see benefits as listed above in many dogs.

It would be fascinating to try Helixor as a first-line treatment in "easier" cancers in large numbers to see what could be achieved. Alas I do not have the time or funding to perform such a study and I hope one of the university oncology departments around the world will investigate the drug in detail soon.

Using Helixor with other drugs

As mentioned, in human medicine Helixor is often used alongside chemo drugs to try for synergistic anti-neoplastic effects and also to ameliorate chemo side effects. I use it the same way in dogs but if the cancer allows us I tend to get through the first cycle rounds of chemo first. This allowed me to assess how well the dog is doing in terms of side effects so that we do not end up mistaking the sometimes profound reactions to Helixor (see later) with chemo side effects.

Having said this sometimes we feel the we have to start everything at once and as long as communication is good and the owners are well aware that signs os sepsis need to be addressed quickly I have not had any disasters.

I am constantly struggling with whether to use steroids (as in lymphoma and MCT protocols) or NSAIDS (most often piroxicam) alongside Helixor. Steroids and NSAIDs are obviously anti-inflammatory and with Helixor we are trying to *provoke* inflammation. If possible I do not mix the either class of drug with Helixor. In cases where it is not possible to avoid the clash I do feel that there is less of an immunostimulatory effect from the Helixor (but they still usually show some reactions) but I don't have a good idea of whether this translates to less effect on the cancer.

I have never had anything that could be described as an adverse drug interaction with any other class of drug.

Treatment of cats

In the first few years of my use of Helixor I did treat about 30 cats. I discontinued use because many of the cats showed a distressing generalized pruritus with use of the drug that led to widespread over-grooming, anorexia and weight loss. I didn't see enough positive responses from the drug to outweigh this negative response. I know that Dr Piper has not had the same experience and still recommends the drug in cats.

How is Helixor used?

The drug comes in glass vials. Each vial contains 2ml and there is "officially" 50mg per ml.

Dr Piper made a decision early on (which I agree with and have continued using) to treat Helixor like insulin and call it a "100 unit per ml" solution the same as most insulins. This is because the drug is given at home by the owners subcutaneously and they will be using insulin syringes. We open the vials (which do not need to be refrigerated before opening) and decant the solution into red-top laboratory tubes for dispensing to the owner. These must be kept refrigerated to reduce the possibility of the fluid becoming contaminated with microbes as doses are withdrawn from the tube. If the fluid becomes cloudy or discoloured then it should be discarded.

The owners get a tutorial from our nurses on how to use a syringe and give injections, just like for insulin in a diabetic patient. Very few owners cannot manage it. We also teach them how to take rectal temperature if the dog will permit it, and most will.

Induction Phase

In this phase the injections are given (in my patients) every 2-5 days, with every 3rd day being the average. The aggressiveness of the patient's cancer will determine the interval, with fast-moving cancers tending to result in treatment every other day.

The reason for therapy including "days off" is twofold. The first is that during the reactive phase (see below) the dogs often seem quite unwell for 12-36 hours. If the injection is given every day they can seem miserable to the owners continuously for up to 7-14 days, and when I was using daily injections I had owners decide to stop treatment because they felt that their pet was suffering too much.

The second reason is that I believe (but have no proof) that there is an "area under the curve" benefit from seeing a long reactive period that is of moderate intensity rather than a short intense reactive period. In my mind (and it is probably not physiologically relevant) it is like the experiment with depot injections of cisplatin for osteosarcoma, where a long-lasting low serum concentration of cisplatin resulted in much better tumour responses than intermittent very high serum concentrations resulting from an IV dose that was cleared quickly. I have no way of proving that this effect occurs with Helixor, but it is somewhat analogous to our vaccination protocols where we space the vaccines out rather than giving them all in three days.

The reactive sub-phase

During the induction phase the vast majority of dogs will show various manifestations of what we feel to be immune system reactions. I tend to ask owners to give the drug in the evening so that a significant portion of the reaction to that dose is going to be while the dog is asleep (or at least the owner is asleep!) and therefore the owner is not so distressed by it. This is optional and if an owner feels strongly that they want to give it at another time of day I do not demur.

The signs of reactions can be;
Fever; this can be as high as 41° and usually the owners are in no doubt that the temperature is abnormal. It may trend up over a period of several treatments, or might be normal and then suddenly jump up and be abnormal. Temperature is measured about 12 hours after injection; some owners are quiet happy to take a temperature every day, and this might be especially useful if the dog is getting chemo too.

Malaise; I call this the 'achy flu period'. The dogs will be, as mentioned, febrile, they will seem lethargic, perhaps stiff and sore, reluctant to exercise, and reluctant to eat in many instances.

Skin swellings; the dogs will also usually during the reactive phase show the development of subcutaneous or intradermal lumps at the injection sites. I say to the owners these are analogous to a bee sting. They come up over a day or two; they are uncomfortable to the touch, quite hard, swollen and may appear reddened on the surface of the skin. Then, over the next 2-3 days they gradually disappear but a new lump will be appearing at the most recent injection site. Although I've never biopsied one of these lumps, I would fully anticipate that they would show a variety of inflammatory cells and vascular responses.

It should be emphasized that these signs of immune system activation spontaneously regress, and do not need treatment. In fact because we are trying to *provoke* the immune system the last thing we want to do is *suppress* these phenomena. I call them effects of the drug, not side effects. It is one of the few times in medicine when an owner calls to say "my dog has a fever and won't get

out of bed" and we can say "good!" Some owners need quite extensive phone support during this time which is normally done by my nurses. As mentioned, if the dog is also on chemo then a revisit and blood counts might be needed to rule out neutropaenia.

I have never seen a neurological side effect, or a gastrointestinal side effect other than anorexia. I have never seen an abscess develop, despite my patients having had (cumulatively) thousands of injections and sometimes I have noted to my horror that owners have used Helixor that looked obviously contaminated by microbial growth.

During the reactive phase (which usually starts at around 5 to 15 units) I ask the owners to give the SAME DOSE each time. Dogs vary, a small number never have a reaction, some will react for 25 consecutive doses. If a dog reacts at 10 units for 7 times it means they will get 8 consecutive doses of 10 units then when the 8th 10 unit dose has failed to produce a reaction they go to the next dose increment and upwards from there.

The reason for thee same dose being used repeatedly is to try to prolong this reactive phase for as long as possible, in the assumption that it is during this phase that some sort of anti-cancer immunity is going to be created.

I usually go; 2.5, 5, 7.5, 10, 15, 20, 25 etc up to 100 units. Then the guidelines from the manufacturers themselves suggest 100, 150, 200, 150, 100 units as the culmination of the induction phase. I have no idea why they recommend this odd crescendo-decrescendo but that's they way the ask you to do it and I have never come up with a reason why not.

Very few dogs will have a second reactive period, either during the rest of the induction phase or during maintenance. If they do then the same advice as above applies; ie give the same dose again until the reactions subside.

Maintenance phase

The dogs get 100 units per week indefinitely. I find that if the dog is doing well owners have no problem justifying the ongoing costs. I never know when to stop. I had one dog in the early days with a metastatic perianal gland adenocarcinoma go into complete remission. The owner was overjoyed and could not thank me enough. She firmly believed that the dog was cured and that I was a miracle worker. Despite my misgivings I agreed to stop the drug. Within weeks the tumour came back with a vengeance and did not respond again. This has led me to suggest indefinite treatment if the owners are willing!

Cost of treatment

It is difficult to give owners precise cost estimates because each dog will have a variable number of reactions and therefore total dose over the induction period will vary. This is not highly significant as the dose is per dog, not per kilo, and the reactions usually happen in the early stages when the number of units is relatively low, i.e. 10 or 15.

Costs for vet time, nursing time and needles etc have to be built in.

Your clinic will have its own overhead structure and costings, but each vial of Helixor (containing 2mls = 200 units) costs approximately $38.00 plus GST. Availability via Dr Chris Piper's own distribution company has been good for more than 15 years but there are some clouds on the

horizon regarding this as the ACVM is looking at the product more carefully in its latest regulatory round so stay tuned for developments.

I usually estimate that six months of treatment that will include the induction phase is likely to cost $1200 to 1500, which is not insignificant but is cheaper than most chemo protocols.

Summary

Helixor is a fascinating product. If I was diagnosed with cancer tomorrow I would almost certainly treat myself with Helixor as well as conventional therapy. I think that its use should be considered in many cancers, as along as owners are fully informed as to our lack of hard data regarding its efficacy.